Research Article

Study of Some Variables Affecting Product Properties of Felodipine Nano Precipitation

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Received: 10-01-2017; **Revised:** 30-01-2017; **Accepted:** 14-02-2017.

ABSTRACT

Felodipine belongs to Class II according to the Biopharmaceutics Classification System, the improving the rate of dissolution will greatly improve bioavailability. Reducing the particle size to nano range will hasten dissolution. Nano precipitation was chosen because it is a one -step simple method that involves the precipitation of a polymer (CMC) or (PVA) in a suitable solvent (Non-solvent); thereby surrounding Felodipine. Different drug: polymer ratios and solvent: antisolvent ratios were utilized in the preparation of Felodipine nanoparticles. Particle size and poly dispersity were measured and found that type of polymer and the ratio of the combination will greatly affect the particle size; PVA produced smaller particle size range and the (1:1) drug: polymer ratio produced the best average particle size. Also, the volume of solvent used greatly affects the particle size so that the (1:10) Solvent: Non-solvent was the best ratio to produce the smallest average particle size.

Keywords: Nano precipitation, Felodipine, Polyvinyl alcohol.

INTRODUCTION

Felodipine is a FDA approved calcium channel blocker, it is almost completely absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of Felodipine is approximately 20% [1].Felodipine,is insoluble in water and is freely soluble in acetone and in methanol[2]. Felodipine belongs to Class II (low solubility high permeability) according to the Biopharmaceutics Classification System; the rate of dissolution will determine the rate of absorption[3, 4]. Therefore; Felodipine nanoparticles were formulated, to improve dissolution rate. Solvent displacement / nano-precipitation method involve the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium. Organic solutions of water insoluble drug will precipitate in water, to maintain fine particle size of the drug (prevent coagulation), a hydrophilic polymer or stabilizer is used. These polymersin the presence of a poor solvent will exist in a non -expanded (coiled) state. Lyophilic polymers become lyophobic by addition of solvents like acetone or alcohol and become desolvated, and precipitate, surrounding the insoluble drug[5]. It is a simple one step operation which offers advantages over other techniques like emulsion –solvent evaporation[6].

MATERIALS AND METHODS

Materials

Felodipine Provizer Pharma. India, Carboxymethyl cellulose (CMC) Hi Media Laboratories India, Polyvinyl alcohol (PVA) JP&SB Converting Services International S.L Spain, Ethanol GCC Analytical reagent UK, Methanol J. T Baker, Netherlands Hydrochloric Acid BDH Chemical LTD UK, Sodium Hydroxide Carlo Erba reagent Spain, Potassium Dihydrogen Phosphate BDH Chemical LTD, UK

Methods

Preparation of Felodipine Nanoparticles:

Felodipine Nanoparticles were prepared by using solvent/Non-solvent precipitation technique (Nano-precipitation method). Felodipine (1mg/ml) was completely dissolved in ethanol. The obtained drug solution was then injected at speed of 1ml/min using syringe infusion pump (Byz-810) into distilled water containing a different (drug: polymer) ratio of the stabilizer (CMC or PVA) with continuous stirring. Precipitation of solid drug particles occurred immediately upon mixing the precipitated nanoparticles are sonicated at 37 °C for 30 min[7].In order to retrieve nanoparticles in dried-powder state water-removal was conducted through freeze-drying system (Labconco, USA) in which the precipitated nanoparticles was lyophilized using vacuum freeze dryer at a controlled temperature of (- 44) °C and the pump operating at a pressure of 2.5 × 10 Pascal over a period of 48–72 hour[8]. The composition and variable condition of preparation of different formulas of Felodipine nanoparticles are listed in table (1).

Characterization of Felodipine Nanoparticles:

Particle Size Analysis

Samples of all prepared nanoparticles were analyzed using ABT-9000 Nano laser particle size analyzer, and particle size distribution curves were obtained. Also the average particle size, polydispersity index (PDI), and the specific surface area (SSA) for each sample were recorded.

Table 1: Composition of Felodipine Nanoparticles Formulas of different Felodipine (F): Polymer ratio and various Solvent: Non solvent ratios, at drug concentration of 1mg/ml of Felodipine

	F:CMC	F:PVA	Solvent :Non Solvent
C1	1:0.5		1:10
C2	1:1		1:10
C3	1:2		1:10
C4	1:3		1:10
C5	1:1		1:5
P1		1:0.5	1:10
P2		1:1	1:10
P3		1:2	1:10
P4		1:1	1:5
P5		1:1	1:15

Polydispersity index is a parameter to define the particle size distribution of nanoparticles obtained from a particle analyzer. PDI is an index of width or spread or variation within the particle size distribution and gives an indication about the long term stability of Nano-suspension. Mono-disperse samples have a lower PDI value, whereas higher values of PDI indicate a wider particle size distribution and the polydisperse nature of the sample. The usual range of PDI values is 0-0.05 (monodisperse standard), 0.05-0.08 (nearly monodisperse), 0.08-0.7 (midrange polydispersity), and >0.7 (very polydisperse) [9].

RESULTS AND DISCUSSION

The specific surface area (SSA) of the particles is the summation of the areas of the exposed surfaces of the particles per unit mass. There is an inverse relationship between particle size and surface area

Table 2: Particle size data of prepared Felodipine nanoparticles

	F:CMC	F:PVA	Solvent :Non Solvent	Particle size average	Polydispersity index (PDI)	Specific surface area (m^2/g)
C1	1:0.5		1:10	200	0.126	9.85
C2	1:1		1:10	133	0.64	15.3
C3	1:2		1:10	897	0.29	2.14
C4	1:3		1:10	1224	0.016	1.56
C5	1:1		1:5	678	0.006	3.25
P1		1:0.5	1:10	224	0.008	9.05
P2		1:1	1:10	50	0.317	37.16
P3		1:2	1:10	1019	0.002	1.82
P4		1:1	1:5	402	0.029	6.05
P5		1:1	1:15	507	0.018	4.59

The results showed that formulas containing CMC displayed midrange polydispersity, while PVA showed mono dispersitymay because CMC is more hydrophilic than PVAwith more hydroxyl groups retaining more water, also CMC is a semi-synthetic , and natural polymers usually show more monodispersity.

Also it has been seen that PVA gave the lowest particle size when used as stabilizer. This could be due to PVA which is high affinity for both hydrophilic and hydrophobic surfaces, this also means that PVA has a higher affinity to adsorb Felodipine than CMC, although CMC is an anionic polymer, and anionic polymers showed better entrapment of drugs like proteins, but the non-ionic PVA showed lower average particle size[10].

Effect of Drug: Polymer ratio

The results show that changing polymer concentration has an impact on Felodipine nanoparticles mean size. Increasing polymer concentration lead to increase in mean particle size but observed only higher than drug: polymer equal ratio. This can be explained that increasing polymer concentration caused more coating of drug particles until certain concentration, where all drug particle are coated with polymer, then increasing polymer concentration would lead to increase the thickness of the

polymer coat around each particle or may lead to aggregation of many particles and increase in the mean particle size

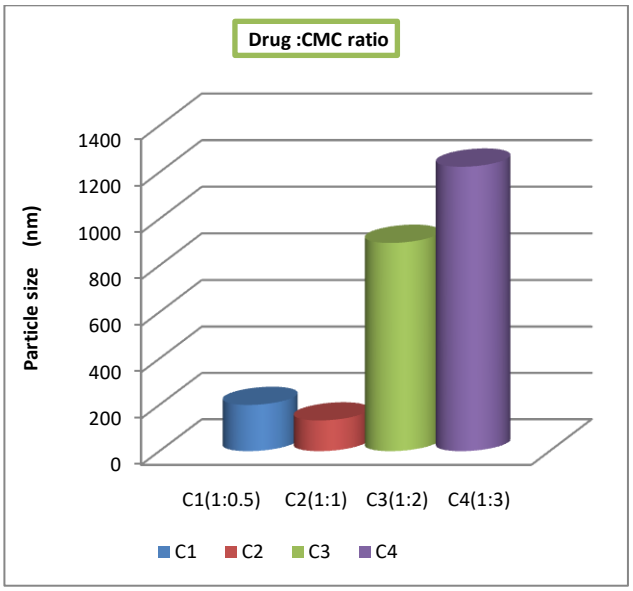

Figure 1: The effect of Felodipine: CMC ratio on the particle size of Felodipine nanoparticles at constant Solvent: Non Solvent ratio (1:10)

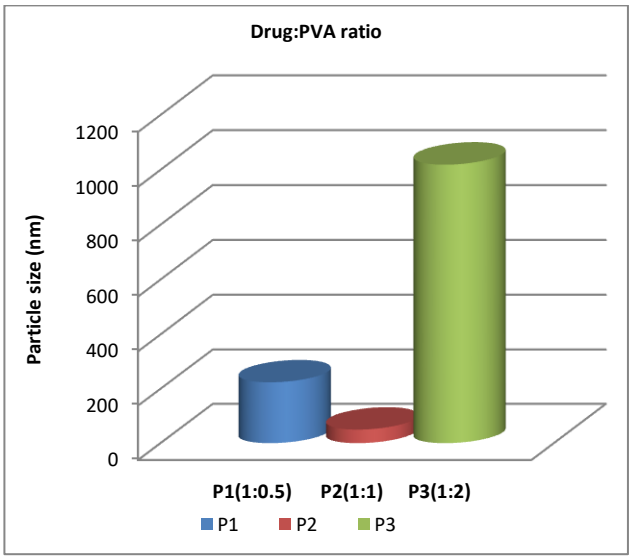

Figure 2: The effect of Felodipine: PVA ratio on the particle size of Felodipine nanoparticles at constant Solvent: Non Solvent ratio (1:10)

Effect of Injected Volume (Solvent: Non-solvent ratio)

The effects of changing the ratio of injected drug solvent solution to stabilizer Non-solvent solution on the mean size of the nanoparticles formed were shown in figure 3,4. It has been shown that the Solvent: Non-solvent ratio 1:10 was the best ratio among the other (1:5 and 1:15) which gave the lowest mean particle size. The same ratio used by Dong *et al* for the preparation of spironolactone nanoparticles as they found that 1:10 ratio gives the lowest particle size [11].

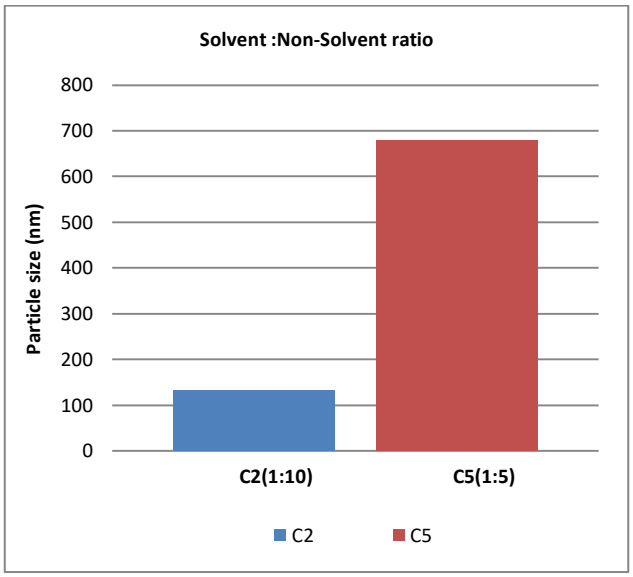

Figure 3: The effect of changing the injected volume of on the particle size of CMC Felodipine Nanoparticles

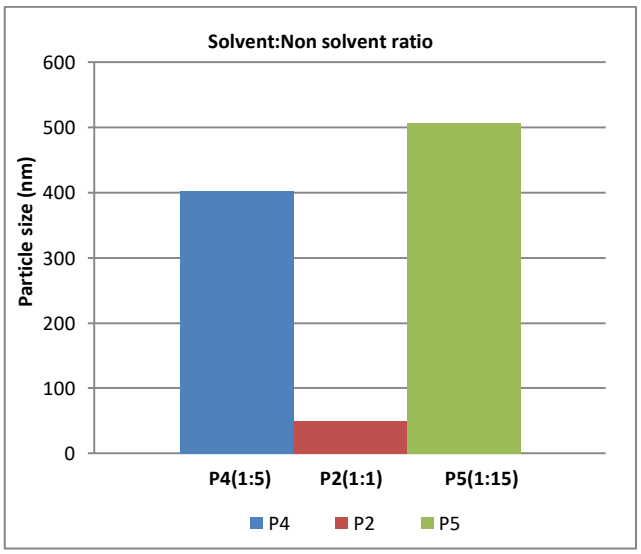

Figure 4: The effect of changing the injected volume on the particle size of PVA Felodipine Nanoparticles

CONCLUSIONS

Felodipine is water insoluble drug, reducing the particle size will speed up dissolution rate, nano precipitation was to reduce the particle size using more hydrophilic polymers like CMC and PVA Felodipine nanoparticles were prepared in which PVA gave the lower average particle size at (1:1) drug: polymer ratio and (1:10) solvent :Non-solvent ratio

Acknowledgments: Authors wish to thank the College of Pharmacy –University of Baghdad for using the lab, to accomplish this work

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Source of Support: Nil, **Conflict of Interest:** None.